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HTA-Report | Summary

The importance of growth factors for the treatment of chronic wounds in the case of diabetic foot ulcers

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Introduction

Chronic wounds represent a serious medical and societal problem. The challenge for medicine and nursing is an adequate care of patients who must be treated for months and partly for years resulting in economic high costs.
Chronic wounds lead to a substantial reduction in quality of life caused by pain and immobility. Social isolation and financial problems may be further consequences.
Due to these psychosocial impacts and often occurring heterogeneous comorbidity wound management is a great challenge for all health care systems. In addition to the medical care provided by several specialists, home care for the patients plays a central role.
One type of chronic wound is diabetic foot ulcer, being a serious problem with an enormous impact in the overall global disease burden due to the increasing prevalence of the disease. 2 to 10 % of patients with diabetes mellitus suffer from foot ulcers with an annual incidence of 2.2 to 5.9 %. Because of long hospital stays, rehabilitation, often required home care and the use of social services diabetic foot complications are costly. Therapy with growth factors could be an effective and innovative add on to standard wound care.
In Germany the active substance becaplermin is approved and sold under the product name Regranex; due to opportunistic sales a treatment with the metabolically active skin graft Apligraf is also possible.

Research questions

Medical research questions

- How effective and safe is the application of growth factors alone for the treatment of diabetic foot ulcers compared to other technologies?
- How effective and safe is the application of growth factors in combination with other technologies for the treatment of diabetic foot ulcers compared to other technologies?

Economic research questions

- What is the cost-effectiveness of growth factors alone for the treatment of diabetic foot ulcers compared to other technologies?
- What is the cost-effectiveness of growth factors in combination with other technologies for the treatment of diabetic foot ulcers compared to other technologies?

Within the scope of the

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Ethical, social and juridical research questions

Which ethical, social and juridical issues are important for the assessment of diabetic foot ulcer treatment with growth factors?

Methods

A systematic literature search for publications in English and German language since 1990 is conducted using the databases MEDLINE, EMBASE, AMED, BIOSIS Previews, MEDIKAT, Cochrane Library – Central, gms, SOMED, CAB Abstracts+CAB, ISTPB+ISTP/ISSHP, ETHMED, GLOBAL Health, Deutsches Ärzteblatt, EMBASE Alert, SciSearch, CCMed, Social SciSearch, Karger-Verlagsdatenbank, Kluwer-Verlagsdatenbank, Springer-Verlagsdatenbank, Springer-Verlagsdatenbank PrePrint, Thieme-Verlagsdatenbank, Derwent Drug File, IPA, gms Meetings, DIQ-Literatur, HECLINET, Hogrefe-Verlagsdatenbank und Volltexte, Thieme-Verlagsdatenbank PrePrint, Krause & Pachernegg Verlagsdatenbank. Especially HTA-reports, systematic reviews and health economic evaluations are searched in the databases Cochrane-Library CDSR, NHS-CRD-DARE, the International Agency for Health Technology Assessment NHS-CRD-HTA, the National Health Service in Great Britain NHSEED and the HTA-database of the German Agency for Health Technology Assessment (DAHTA). Two reviewers independently check the identified literature regarding subject and predefined inclusion and exclusion criteria. Studies about the safety and efficacy of therapies with growth factors for diabetic foot ulcers are included. While using full economic evaluations for answering the economic questions cost values are adjusted to the price level of 2008 and converted into Euro to establish comparability between the international studies. A review and an assessment of the quality of publications are following methods conforming to widely accepted standards for evidence-based medicine and health economics.

Results

We identified 25 studies fulfilling the inclusion criteria, in detail 14 randomized controlled trials (RCT) covering medical evaluations, nine cost-effectiveness analyses and two meta-analyses.

Six RCT compared standard wound care plus becaplermin with standard wound care alone or extracellular wound matrix, two RCT compared recombinant human epidermal growth factor rhEGF with placebo, one study compared basic fibroblast growth factor bFGF with placebo, four studies compared the metabolically active skin graft Dermagraft and standard wound care with standard wound care alone and one study compared the metabolically active skin graft Apligraf and standard wound care with standard wound care alone. Study durations range from twelve to 20 weeks and the study populations included between 17 to 382 patients, with an average of 130 patients, median 90 patients.

The treatment with becaplermin compared to placebo showed an advantage concerning the proportion of patients with complete wound healing with statistically significant differences and with a greater amount of evidence (higher number of studies) for the concentration of 0.01 % than 0.003 %. Even the time to complete wound healing is clearly shorter for patients with becaplermin treatment with statistically significant group differences.

In the comparison of becaplermin with the extracellular wound matrix OASIS a trend to the detriment of becaplermin could be identified regarding the proportion of patients with complete wound closure and the time to complete wound closure which do not show statistical significance.
The treatment with rhEGF in the concentrations of 0.04 % and 0.015 % compared to standard wound care resulted in a shorter time to complete wound closure after rhEGF treatment, and rhEGF in the concentration of 0.015 % showed advantages concerning the proportion of patients with complete wound closure; all group differences were statistically significant.
There was no benefit for the treatment with bFGF.
The application of Dermagraft once a week for eight weeks compared to standard wound care alone showed an advantage in the proportion of patients with complete wound closure and also in the time to complete wound closure with statistically significant group differences. For the application of Apligraf compared to standard wound care only regarding the proportion of patients with complete wound closure an advantage in favour of Apligraf could be identified.
In four out of 14 studies the proportion of adverse events was 30 % per study group with no difference between the treatment groups. The methodological quality of the studies was affected by significant deficiencies: partly not blinded study conduction, missing information about a concealed treatment allocation and unclear or missing descriptions of the randomization method and intention-to-treat analysis.
The results of the cost-effectiveness analyses of all health economic evaluations showed becaplermin being cost-effective, whereas no obvious statement can be made regarding Dermagraft and Apligraf because of inconsistent cost bases and incremental cost-effectiveness ratios. Depending on the publication both products are either cost effective or not, causing difficulties for decision makers.
No publications for the assessment of social, ethical or juridical issues could be found.
Under certain conditions treatment with becaplermin in Germany is refundable. The German Federal Joint Committee defines in its medicine directive, that the application of becaplermin is only indicated “if the treatment of diabetic neuropathic ulcers with intense and adequate wound care including total pressure relief was not successful.” Therefore becaplermin is only second line therapy. Apligraf is approved in Switzerland and the USA but due to opportunistic sales the access to treatment is also possible in Germany.

Discussion

Taking into consideration the small to very small sample sizes and other methodological flaws with high potential of bias the validity of the results with regard to effectiveness and cost-effectiveness has to be considered limited.
Furthermore, the comparability of the studies is negatively affected by differences in standard wound care, various surgical procedures, different frequencies of debridements during the study course and the individual experience of the investigators with difficult to heal wounds. Additional variability can be attributed to different methods for pressure relief, wound care and strictness of infection control between hospitals, clinicians and nursing staff.

The duration of studies with a maximum of 20 weeks and follow-up periods in only four of the included studies is not long enough to assess the sustainability of the intervention and the surveillance of ulcer recurrences or possible treatment related adverse events like development of malignancy.
Despite the short study durations the modelings continuously showed treatment with becaplermin being cost-effective with either small additional costs per effect measure or even cost savings. Based on the present publications statements concerning the cost-effectiveness of Dermagraft are difficult to derive because the two publications show different costs per piece. The cost-effectiveness of Apligraf is equally vague given the contradictory results of the two studies.

Conclusions

There are indications of an advantage for the add-on therapy with growth factors in diabetic foot ulcers concerning complete wound closure and the time to complete wound healing. Prevention and treatment of diabetic foot ulcers is extremely complicated. Many factors are important for the development of diabetic foot ulcers and all of them have to be considered. The current available evidence is not satisfying for clinicians who are forced to make a choice. Even in recommendations for standard wound care there are variations. The existing evidence concerning alternative therapies is still weaker.
Hence, further studies about the treatment of diabetic foot ulcers with growth factors alone or in combination with other technologies of high methodological quality with adequate sample sizes are necessary, especially regarding the demographic change and the growing prevalence of diabetes mellitus leading to higher prevalence rates of diabetic foot ulcers.
In addition to the investigation of clinical outcomes future studies should also examine the patient-relevant parameters quality of life, satisfaction, acceptance, tolerance of and compliance with treatment. Moreover, stratifications of study populations concerning type of diabetes or ulcer location should be undertaken.